

Immunodeficiency and other clinical immunology

Netherton's syndrome: A syndrome of elevated IgE and characteristic skin and hair findings

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Netherton's syndrome is a rare symptom complex characterized by greatly elevated IgE levels with atopic manifestations, an ichthyotic skin disorder (ichthyosis linearis circumflexa and/or congenital lamellar ichthyosis), and the characteristic hair abnormality trichorrhexis invaginata. It may be confused with atopic dermatitis but does not respond to topical corticosteroid treatment. Netherton's syndrome is therefore of considerable importance to allergists. In this article we report the results of the clinical and immunologic evaluation of a previously unreported patient who responded to treatment with 12% ammonium lactate lotion and management of his allergic disease. Furthermore, we have reviewed the English literature and compared the findings in our patient with those of 43 other reported patients. Our patient shared the features of other previously reported patients with this disorder. We conclude that this disease should be included among the other disorders with elevated IgE. Patients may benefit from evaluation and treatment of their allergic symptoms and topical skin treatment with ammonium lactate. (J ALLERGY CLIN IMMUNOL 1995;95:116-23.)

Key words: Netherton's syndrome, ichthyosis linearis circumflexa, trichorrhexis invaginata, IgE, atopy

The disorders commonly associated with greatly (>1000 IU/ml) elevated levels of IgE include Wiscott-Aldrich syndrome, thymic hypoplasia (DiGeorge syndrome), cellular deficiency with immunoglobulins (Nezelof syndrome), selective IgA deficiency, and the hyperimmunoglobulinemia E (Buckley's) syndrome.¹ We believe that Netherton's syndrome (NS) should be added to this list. In this report we review the clinical features of a previously unreported patient under our care in the context of those cases already reported.

CASE REPORT

C.C., now 3 years of age, was the term product of an uneventful pregnancy with a birth weight of 7 pounds, 0

Abbreviations used

ILC:	Ichthyosis linearis circumflexa
nl:	Normal limits
NS:	Netherton's syndrome
TI:	Trichorrhexis invaginata

ounces. There was no history of consanguinity. A generalized erythematous rash was noted at birth. A punch biopsy specimen (Fig. 1) was interpreted as showing nonspecific inflammation, and a clinical diagnosis of scalded skin syndrome was made. The nursery course was complicated by hypernatremic dehydration with a serum sodium level of 153 mg/dl. Multiple formula intolerances were noted, but he was able to tolerate Alimentum, a highly hydrolyzed infant formula, with minimal allergenicity. He was hospitalized at 5 weeks of age for treatment of gastroenteritis. Continued skin and hair problems led to a diagnosis of ichthyosis linearis circumflexa (ILC) (Netherton's syndrome) at 15 months of age, by Jack L. Leshner, MD, at the Medical College of

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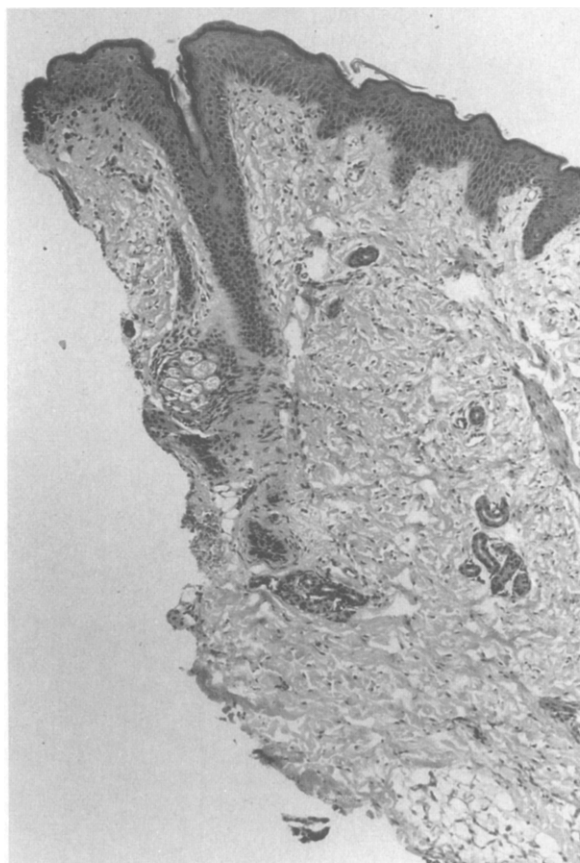


FIG. 1. Low-power hematoxylin-eosin-stained punch skin biopsy specimen. The epidermis shows mild hyperkeratosis and parakeratosis. The rete ridges are elongated.

Georgia; 12% ammonium lactate lotion was prescribed. He was subsequently lost to follow-up because of a move to Alabama and was receiving no therapy when he was first seen at the University of South Alabama.

Problems when first seen by us included a chronic pruritic rash and intolerance to milk (vomiting) and crab (swelling of lip); the patient would not eat eggs. He had frequent clear rhinorrhea and sneezing, with a watery to yellowish eye drainage. He had recently had an ear infection. There were no symptoms referable to the chest. The scalp hair was sparse and broke off easily. He was unable to tolerate the heat outdoors in the summer, apparently because of inability to perspire.

Further history revealed aggravation of nasal symptoms with dust exposure and large local reactions to fire ant. There was a history of "sinus trouble" on both sides of the family, but the patient had no relatives with skin disorders.

Physical examination revealed an irritable child with height at the 25th percentile and weight at the 10th percentile. The skin was xerotic with a scaly rash; many of the scales were double-edged (ILC) (Fig. 2). The hair



FIG. 2. Volar aspect of elbow, showing ILC in our patient, C.C.

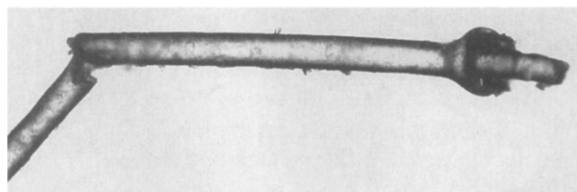


FIG. 3. Trichorrhexis invaginata. On the left, the hair shaft is fractured. The right end shows typical "ball and socket" of TI; the distal portion of the shaft is invaginated into the proximal portion.

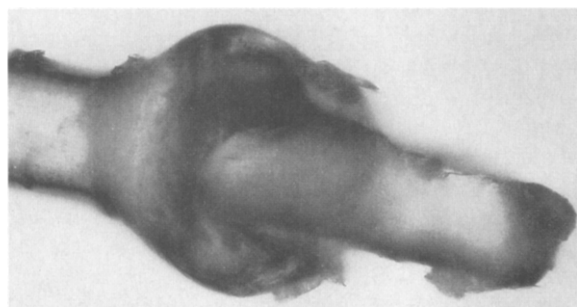


FIG. 4. Higher power magnification of "ball and socket."

was sparse and dysplastic, with trichorrhexis invaginata (TI) (bamboo hairs) (Figs. 3 and 4) and an extensive dry adherent "cradle cap." (Fig. 5) The eyebrows were sparse, especially laterally, whereas the eyelashes, nails, palms, soles, and teeth were normal in appearance. There was moderate reddening of the palpebral conjunctivae without papillae. The tympanic membranes were dull in appearance, and tympanograms were flat for both ears. The turbinates were mildly enlarged and pallid in appearance. The lungs were clear as determined by auscultation. Evaluation at the pediatric clinic revealed developmental delay.

Skin prick testing revealed positive reactions to ex-



FIG. 5. Appearance of scalp in patient C.C.

tracts of *Dermatophagoides pteronyssinus*, soy, egg, peanut, corn, white oak, cat, and dog, but not to crab. Sinus series revealed pansinusitis. An intradermal skin test with *Candida albicans* 1:100 produced an induration of 3×3 mm at 48 hours. In our experience this is an unusually small reaction in a patient this age, suggesting some decrease in cellular immune responses.²

The patient was started on a regimen of beclomethasone nasal spray, hydroxyzine, amoxicillin-clavulanate for treatment of sinusitis, selenium sulfide shampoo, and 12% ammonium lactate lotion (Lac-Hydrin 12%). At a follow-up visit 3 weeks later, there was considerable improvement in the skin (Fig. 6), which has subsequently improved further with continued lactate treatment. The scaliness in the scalp was also somewhat diminished. A Waters' view of the sinuses was clear, and the tympanogram was normal. An unblinded peanut challenge with roasted peanuts produced no clinical symptoms, but the parents later reported swelling of the lips after the patient ate boiled peanuts.

Laboratory testing revealed a normal blood count without eosinophilia. The IgE level was 15240 IU/ml, IgA 140 mg/dl (normal limits [nl] 14 to 123), IgM 68 mg/dl (nl, 43 to 173), IgG 969 mg/dl (nl, 709 to 1075). IgG subclasses were normal except for an IgG₄ level of 87 mg/dl (nl, 10 to 37). Diphtheria and tetanus antibody titers were within the protective range; there were low but detectable pneumococcal antibodies to three of four types, and fourfold or greater rises in titer to two of four types after immunization with 21-valent pneumococcal vaccine. The blood type was A with a normal 1:64 anti-B titer. Thus humoral responses appeared to be intact. The complement C5 and CH50 values were normal at 14.2 mg/dl and 76% of standard (repeat, 101% of standard) respectively, and the complement C2 was mildly elevated at 4.0 mg/dl (1.6 to 3.6 mg/dl). Because of the high IgE level, an interleukin-4 level was ordered; this was reported as not detectable. The HLA-D types were DR4, 13 (DR52, 53), DQ1, 3. Lymphocyte phenotyping was normal with 1733 CD4, 1411 CD8, and 403 B cells per cubic millimeter. Ia (HLA-DR) and interleukin-2R markers were 6% (normal 0%) and 8% (normal 0%) of

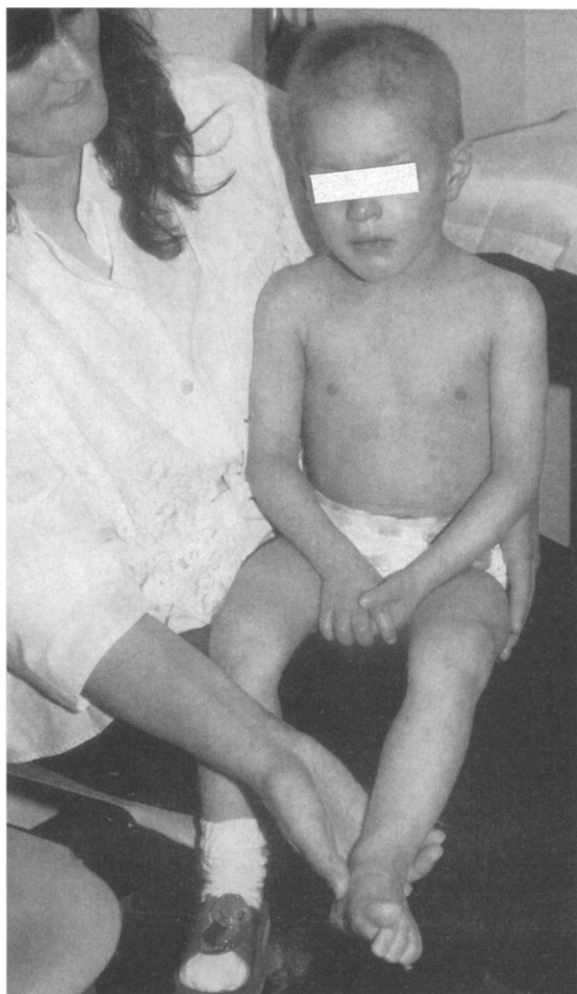


FIG. 6. Improvement in skin after treatment with 12% ammonium lactate lotion in patient C.C. The eyebrows are sparse laterally, and the lips appear prominent.

peripheral blood lymphocytes, respectively, indicating the unusual presence of activated lymphocytes in the peripheral blood. However, α -interferon was undetectable, suggesting that a chronic viral infection was not present. Natural killer cells were estimated to be in the normal range, at 6% to 14% of lymphocytes. Urinary amino acid and sugar excretion was normal. Neutrophil function tests were not performed.

REVIEW OF LITERATURE

The historical context

NS, originally described by Dr. E. W. Netherton in 1958,³ is a disorder consisting of ichthyosis (ILC and/or congenital lamellar ichthyosis), hair shaft defects including TI, and, usually, atopic manifestations. TI is considered characteristic of the disease; patients with similar skin findings but without TI have been generally excluded from reviews.

TABLE I. Common findings in 44 cases of Netherton's syndrome

Finding	Number	Percent
TI	44	100
ILC	35	80
Other congenital ichthyotic erythroderma	9	20
Female sex	24	55
Inflammatory findings on biopsy	21	48
Sparse eyebrows	18	41
Scalp scaling	17	39
Asthma and/or allergic rhinitis	15	34
Food allergy	14	32
Recurrent infections	13	30
Lichenification/eczematoid changes	12	27
Decreased growth	12	27
Normal immunoglobulin levels	11	25
Family history of atopy	11	25
Positive skin test or RAST results	10	23
Aminoaciduria at any time	10	23
Improvement in hair growth with time	8	18
Sibling cases	8	18
Decreased IQ or mental development	7	16
Decreased weight for height	7	16
Eosinophilia	7	16
Palm or sole involvement	7	16
IgE level >900 IU/mL	5	11
Seasonal changes in skin condition	5	11
Absence of white dermographism	5	11
Pruritus	5	11
Excess vellus hair	4	9
Normal karyotype	4	9
Hypernatremia in infancy	3	7
Consanguinity	3	7
Decreased bone age	3	7
Heat intolerance	3	7
Decreased immunoglobulin levels	3	7
Abnormal nails	3	7
Prominent lips	3	7
Bullous changes	2	5
Elevated immunoglobulin levels	2	5
Abnormal teeth	2	5

Data is compiled from literature review.³⁻³³

Case reports and reviews of NS have appeared primarily in the dermatology literature, with the result that it is not well known among allergists. We have reviewed all of the 43 known case reports in the English language with documented TI.³⁻³³ Salient features of these reports and of the findings in our patient are presented in Table I. Several of the case reports described relatives of patients with NS who appeared to have NS, but without documented TI. There were also cases in other languages but with English abstracts available through the National Library of Medicine. These cases

were not included in Table I but will be reviewed as appropriate in the discussion to follow.

Inheritance pattern

Consanguinity in two reports^{6,8} and the occurrence in siblings* would suggest an autosomal recessive mode of inheritance. A predominance of female patients has been noted in previous reviews, but 20 of the 44 patients are male. Karyotyping has as yet found no abnormality.

*References 6, 8, 18, 26, 27, and 34.

Skin and hair abnormalities

The skin is noted to be abnormal at birth or within the first month of life with a generally nonbullous congenital ichthyosiform erythroderma, which may resemble acrodermatitis enteropathica or Leiner's disease; hypernatremic dehydration during the neonatal period has been noted in previous case reports, presumably caused by excess fluid loss through the abnormal integument.^{16, 34} There may be an increased neonatal mortality rate among patients with NS; three reports note that a sibling with similar skin findings died in infancy.^{16, 20, 22} In most cases the skin disorder gradually evolves into ILC, which appears as erythematous migratory patches surrounded by serpiginous double-edged scales; the lesions have been described as migrating at a rate of 0.5 mm/day.⁵ These large double-edged scales (Fig. 2) are usually found in flexural areas of untreated patients; patients also have skin findings suggestive of atopic dermatitis, such as lichenification and scaling. ILC, originally described by Comèl,³⁵ may be seen as an isolated finding. Conversely, ILC lesions are not always seen in NS and when present may be subtle, with eczematoid²⁷ or ichthyotic⁶ features continuing to predominate. A remarkable erythroderma may be seen with infection¹⁹ or excitement.³³ Pruritus appears to be an inconstant feature.³⁶ Decreased sweating with heat intolerance is thought to be due to plugging of sweat ducts.²⁴ The scalp is usually quite scaly, but nails and teeth are usually not involved. Palms and soles are usually reported as normal but are sometimes described as hyperkeratotic. White dermographism is not present, but intracutaneous injection of methacholine may produce a delayed blanching.²⁹

The underlying skin defect in NS is incompletely understood. Routine biopsy specimens show few abnormalities other than ichthyotic changes, but a mononuclear perivascular infiltrate in the papillary dermis is consistently noted. Transmission electron microscopy has shown abnormalities in the desmosomato-filament complex and membrane-coating granules with loss of lamellar structure of the horny layer, round bodies in the prickle cells, and lipid droplets in the stratum corneum cells.^{29, 37, 38} Elevated *n*-alkane levels have been reported in one case, but this finding also appears to be common in other hereditary ichthyoses.³⁹ Elastase-inhibiting activity is also elevated.⁴⁰ Other reports have stressed the presence of eosinophilic material²² and apparent extravasated serum protein²⁹ in the epidermis.

Expression of the hair abnormalities appears to

differ greatly among patients. In some cases hair abnormalities may not be recognizable in the neonatal period.¹⁶ In addition to TI, pili torti (twisted hair) and trichorrhexis nodosa (fractured hair) may also occur. In some cases only the vellus²¹ or eyebrow^{4, 5, 8, 41} hairs are grossly abnormal, whereas in others the hair defect is severe and obvious to the casual observer, as in our patient. Sparsity of the eyebrows, especially laterally, has been noted in many reports. Improvement in the hair abnormalities and growth frequently occurs during later childhood and adolescence,^{6, 8} such that in adults only the eyebrow or vellus hair may be affected. It seems likely that some cases of NS that are first seen in adulthood are missed because of complete regression of the hair lesions.²⁵ An extensive review of the hair shaft abnormalities has been published.²⁸ The hair defects appear to be due to intermittent incomplete formation of disulfide bonds in the keratogenous zone.⁴¹ There is no known treatment for the hair defects other than the use of a wig. TI was originally termed "bamboo hair" by Netherton,³ but this term has been used for trichorrhexis nodosa and therefore may be confusing.

When examining the hair for trichorrhexis nodosa, the examiner should cut (rather than pluck) hairs from several areas of the scalp, as well as the eyebrows and vellus hair. The invaginations are frequently visible to the naked eye. The hairs may be examined under the microscope without staining (Figs. 3 and 4).

Case reports and reviews of NS have emphasized that the presence of TI is required to make the diagnosis. However, the manifestations of the disorder are quite protean even in the same patient over time. Neither the skin nor the hair may have a characteristic appearance at birth, and by adulthood the hair defects may have disappeared. We suggest that an adult who is first seen with ILC, atopy, and a history of a hair disorder in childhood be considered to have NS even if scalp, eyebrow, and vellus hair are normal. Similarly, a neonate with an ichthyotic skin disorder, who has a sibling with NS, should be considered to have NS until the clinical course indicates otherwise.

Immunologic abnormalities

The laboratory data regarding the immune status of patients with NS are scant. Only five reports have documented the IgE level; these range from 982 to 15,302 IU/ml, with a geometric mean of 4751 IU/ml including our case.^{8, 10, 13, 18} Hypogammaglobulinemia and hypergammaglobulinemia

have been reported, but most patients with NS have had normal immunoglobulin levels. Abnormal neutrophil chemiluminescence has been noted in one case.¹⁰ One report has documented normal lymphocyte numbers and stimulation indices,¹⁰ whereas unresponsiveness to recall antigens and dinitrochlorobenzene has been noted in another.⁴²

We interpret the previous reports and our data as compatible with the speculation that patients with NS have chronic antigenic stimulation, perhaps caused by food antigens, with a prominent IgE and IgG₄ response. Delayed hypersensitivity responses may be relatively decreased. These responses are not dissimilar to those of patients with atopic dermatitis and hyperimmunoglobulinemia E syndrome.⁴³

Chronic upper respiratory tract and staphylococcal skin infections are found in less than half of the reported cases, and an increased incidence of deep tissue infections has not been reported. There may be increased susceptibility to skin cancers.^{44, 45} One patient with NS, treated on a long-term basis with oral glucocorticosteroids, died of vaccine-associated poliomyelitis.¹²

The immunologic abnormalities of most patients with NS have not been evaluated. However, elevations of serum IgE have been consistently noted. Thorough evaluation of future cases may reduce confusion in this area.

Growth and development

Short stature has been noted in 12 patients and poor nutritional status in seven. This includes several patients, not originally reported as having abnormal growth, who were later traced by a reviewer and found to be unusually short or poorly nourished.¹¹ In addition, one patient said to be normally developed had measurements placing him just below the 3rd percentile for height and well below the 3rd percentile for weight.²⁵ Three of the patients with short stature have been noted to have a delayed bone age.^{4, 11, 25} In one patient short stature disappeared by the age of 13.¹¹ One patient with short stature was noted to have recurrent diarrhea,⁵ whereas another patient with recurrent diarrhea whose growth status was not reported had normal intestinal biopsy results.³¹

The incidence of mental retardation appears to be increased in NS; seven reports have found decreased IQ or developmental delay. In these cases one patient had seizures,²⁸ and one had an abnormal electroencephalogram without overt seizures.²² It is possible that undetected neonatal hypernatremia leads to brain damage in such cases.

However, the two other surviving patients who had documented neonatal hypernatremia were reported as having normal development.^{16, 19}

Allergy

A reaction to foods, particularly nuts, is a commonly reported manifestation of allergy. In some cases the patient may manifest a delayed skin response similar to that seen in atopic dermatitis,^{5, 26, 27} but more often the literature has reported anaphylactoid reactions. Respiratory allergy, including asthma, has not been emphasized but appears to occur at least as frequently as food allergy. Peripheral eosinophilia is common. It is likely that atopic symptoms are underreported, because most patients have not been examined by an allergist, and many patients were still in the preschool age group when their cases were reported. Positive skin test or RAST responses to environmental and/or food allergens have been noted in 10 cases including the one presented here. As in our patient, respiratory allergy may be complicated by sinusitis, which appears to be amenable to antibiotic therapy.

Other features

Aminoaciduria has been reported in 10 patients. However, no consistent pattern of amino acid excretion has been noted, and individual patients may have aminoaciduria at one time but not another. It seems likely that at least some instances of aminoaciduria are due to renal effects of systemically absorbed topical corticosteroids.⁴⁶

Other abnormalities reported in individual patients with NS or apparent NS include hypoplastic left heart syndrome,¹⁶ hydronephrosis,¹⁷ and infantile pyloric stenosis.²²

Relationship to atopic dermatitis and other elevated IgE syndromes

NS has many similarities to atopic dermatitis. These include a frequent eczematoid appearance, elevated IgE levels, onset in infancy, decreased delayed hypersensitivity responses in some patients, frequent pyogenic superinfection, concomitant respiratory allergies, and possible exacerbation by food allergens. We believe that at least some of the nutritional and growth problems of these patients are due to food allergies. Early allergy intervention including dietary management and avoidance of inhalant allergens might ameliorate skin, nutritional, and respiratory symptoms.

NS should be distinguishable from atopic dermatitis and the other elevated IgE syndromes if the

patient is seen after infancy and during childhood. The appearance of the dermatitis and the hair abnormalities are distinctive at that time. Unlike atopic dermatitis, there is no white dermographism. Unlike Wiscott-Aldrich syndrome, there is no thrombocytopenia, and most reported patients are female. Unlike patients with DiGeorge syndrome, patients with NS do not usually have dysmorphic facies or parathyroid or cardiac abnormalities. Although delayed hypersensitivity responses may be diminished as in Nezelof syndrome,⁴² normal lymphocyte numbers and stimulation indices have been reported.¹² Our patient had a small but positive delayed hypersensitivity response to *Candida* species and normal immunoglobulin responses to immunization. Deficiency of IgA has not been reported in NS. Finally, unlike hyperimmunoglobulinemia E syndrome, there does not appear to be an increased incidence of deep tissue infections.

Treatment

Corticosteroid treatment of the skin lesions is often unsuccessful. Furthermore, these patients may be particularly susceptible to adverse effects of corticosteroids. Topically applied corticosteroids may be systemically absorbed in unusual amounts, producing Cushing's syndrome,⁴⁷ and fatal vaccine-associated poliomyelitis has been reported in a patient receiving low-dose oral corticosteroids.¹² Etretinate,^{8, 14, 30} psoralen ultraviolet A-range therapy,²⁴ and cyclophosphamide⁴² have been reported as producing improvement, but their potential toxicity makes these modalities less than desirable for long-term therapy. Ammonium lactate lotion (Lac-Hydrin 12%), however, appears to produce excellent improvement in the appearance of the skin in many patients without known long-term adverse effects.^{32, 48} Because of the report of a case of vaccine-associated polio,¹² inactivated poliovirus vaccine may be preferable to live vaccine for patients with NS and family members.

CONCLUSIONS

NS may be confused with atopic dermatitis. The skin and hair abnormalities of NS may be interpreted as being caused by intermittent disruption of the normal keratinization process, but the underlying cause of this syndrome, as with the other syndromes with elevated IgE, remains obscure. Autosomal recessive inheritance and elevated IgE levels are compatible with a defect in a regulatory

gene for IgE production. It seems likely that abnormal T-cell responses, similar to those found in atopic dermatitis, are present. However, other interpretations, such as a defective intestinal mucosal barrier leading to excess absorption of food antigens, are also tenable. Although eosinophils have not been noted in biopsy specimens, the inflammatory changes, eosinophilic material²² and apparent extravasated serum protein²⁹ in the tissue, together with the rapid evolution of the lesions, pruritus, and peripheral eosinophilia, are not incompatible with allergic involvement in the skin disorder.

Patients with NS may benefit from an allergy evaluation. Atopic manifestations appear to be responsive to allergen avoidance and medication, whereas the skin disorder responds to therapy with lactic acid rather than topical corticosteroids, which may be contraindicated in this disorder.

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